

Overview of reported adverse drug reactions in association with drug- substitution between oral contraceptive pills

Introduction

In the Quarterly Report 2006-4 Lareb sent an overview to the Medicines Evaluation Board (MEB) concerning the reports about substitution with the oral contraceptive pill Rigevidon[®] [1].

From June 2007, the Marketing Authorization Holder (MAH) Apothecon withdrew Rigevidon[®] from the market under its original name and replaced it with the generic name ethinylestradiol/ levonorgestrel 0,03/0,15 Apothecon[®] [2]. This oral contraceptive pill contains 150 µgram levonorgestrel and 30 µgram ethinylestradiol [3]. Within three months after the introduction of the Apothecon generic, it reached a market share of over 31%, which was more than half over the market share of Rigevidon[®] in the first quarter of 2007 [2].

Other “one phase” oral contraceptives containing ethinylestradiol/levonorgestrel on the Dutch market are Microgynon[®] (‘20’, ‘30’ and ‘50’), Stederil[®] ‘30’, Elenore[®] (‘sub-50’ pill), Lovette[®] (‘sub-30’ pill) and a variety of generic products.

Because of a substantial number of reports of adverse reactions after drug-substitution between oral contraceptive pills, we give an overview of the reports received by the Netherlands Pharmacovigilance Centre Lareb for the “one-phase” oral contraceptive pills containing ethinylestradiol/levonorgestrel.

The reports of break-through bleeding after substitution of oral contraceptives will be highlighted in this overview since they make up a large portion of the reports Lareb received.

Break-through bleeding is an unscheduled bleeding or spotting which occurs while taking active contraceptive hormones, except bleeding that begins in the hormone-free interval and continues through days 1 to 4 of the subsequent active cycle [4]. Unscheduled bleeding occurs in up to 30 percent of women initiating OCs, but decreases to less than 10 percent by the third month of use. Randomized trials have shown that unscheduled bleeding is slightly higher with the lowest dose OCs (20 mcg ethinylestradiol [EE] component) than with 30 to 35 mcg EE pills. There is no evidence that unscheduled bleeding is associated with decreased efficacy, even with the lowest dose products, as long as the woman takes her pills consistently (ie, no missed days and at the same time every day) [4].

Reports

On 25 August 2012 the Lareb database contained 149 reports of adverse drug reactions related to substitution of one oral contraceptive pill by another oral contraceptive pill. The ATC code for these drugs is G03AA07. The MedDRA[®] Preferred Term that is used to document these reactions in the Lareb database is “Therapeutic response unexpected with drug substitution”.

The number of reports per drug on the level of the HPK-code (*Handels Product Code* or commercial product code) [5] is given in table 1.

Table 1. Number of reports of substitution reaction with the separate OAC's with ATC code G03AA07.

HPK code	Number of reports	Drug name
223107	1	Microgynon 50

HPK code	Number of reports	Drug name
234664	12	Stediril 30
1677500	87	Rigevidon
1873970	40	ethinylestradiol/levonorgestrel 0,03/0,15 Apothecon
1937081	2	ethinylestradiol/levonorgestrel Sandoz 0,02/0,1 mg
2028115	2	levonorgestrelum/ethinylestradiol 0,15MG/0,030MG
2105799	2	ethinylestradiol/levonorgestrel WEC 0,03/0,15MG
2219492	2	ethinylestradiol/levonorgestrel Sandoz
unknown	1	ethinylestradiol/levonorgestrel
Total	149	

Of the 149 received reports, 55 included the MedDRA[®] Lower Level Term (LLT) break-through bleeding as an adverse drug reaction.

The original drug that the patient was using and the product she was switched to when the reaction occurred are listed in table 2, including the number of reports.

Table 2. Oral contraceptive drugs used before and after the switch and the number of reports about break-through bleeding

Drug before substitution	Drug after substitution	Number of reports of break-through bleeding
Microgynon 30	Rigevidon	29
Microgynon 30	ethinylestradiol/ levonorgestrel 0,03/0,15 Apothecon	12
Microgynon 30	Stediril 30	8
Stediril 30	ethinylestradiol/ levonorgestrel 0,03/0,15 Apothecon	3*
Microgynon 30	ethinylestradiol/ levonorgestrel WEC 0,03/0,15mg	1
ethinylestradiol/ levonorg pch tab omh 0,03/0,15mg	ethinylestradiol/lev onorgestrel WEC 0,03/0,15MG	1
Unknown	Rigevidon	1

* One report contains information about 3 patients

As mentioned in the introduction; the drug Rigevidon[®] is now marketed under the name ethinylestradiol/levonorgestrel 0,03/0,15 Apothecon[®]. Lareb received 12 reports of break-through bleeding which occurred after a patient was switched from Microgynon 30[®] to ethinylestradiol/levonorgestrel 0,03/0,15 Apothecon[®] and 3 reports after a switch from Stediril 30[®] to the Apothecon product. A positive dechallenge was reported 4 times, two times with a positive rechallenge. The reported latencies varied from 1 day to 1 month after the switch to ethinylestradiol/levonorgestrel 0,03/0,15 from Apothecon.

There were 172 other reported adverse drug reactions besides break-through bleeding. Table 3 shows the most reported adverse drug reactions.

Table 3. Other adverse drug reactions reported besides break-through bleeding

System Organ Class	Number of reports	Most mentioned preferred terms
Gastrointestinal disorders	42	Abdominal pain, nausea
Nervous system disorders	42	Headache
Psychiatric disorders	27	Mood swings, depression
Reproductive system and breast disorders	25	Menorrhagia, breast pain
Skin and subcutaneous tissue disorders	36	Acne, rash

Other sources of information

SmPC

The SmPC's of Stediril '30'[®] [6] and ethinylestradiol/levonorgestrel WEC[®] [7] mention break-through bleeding in section 4.8 as the most frequently reported adverse drug reaction which occurs in more than 10% of women. All SmPC's mention in section 4.4 that irregular bleeding can occur during the use of combined oral contraceptives, especially during the first few months.

Literature

In general, there are numerous studies that have looked at possible issues with drug-substitution. In 2009, the FDA published a study which evaluated how well the bioequivalence measures of generic drugs approved in the US over a 12-year period compare with those of their corresponding innovator counterparts. They found that in nearly 98% of the bioequivalence studies conducted during this period, the generic product AUC differed from that of the innovator product by less than 10% [8].

A study specifically looking at interchangeability of low-dose oral contraceptives does not include oral contraceptives that are currently marketed in the Netherlands [9].

Databases

On October 2nd 2012 the database of the Netherlands Pharmacovigilance Centre Lareb contained 149 reports of ethinylestradiol/levonorgestrel (ATC G03AA07) associated with the MedDRA Preferred Term (PT) "Therapeutic response unexpected with drug substitution", which was reported disproportionately (ROR = 24.2, 95% CI 20.0 – 29.0).

Data of the database of the Uppsala Monitoring Centre of the WHO are of limited value since it is not clear which brand of oral contraceptive pill, containing levonorgestrel and ethinylestradiol, has been used.

Prescription data

The number of patients using an oral contraceptive containing ethinylestradiol/levonorgestrel in the Netherlands is shown in table 4. Unfortunately the GIP database of the College for Health Insurances does not specify the brand of the drug.

Table 4. Number of patients using methylphenidate in the Netherlands between 2007 and 2011 [10].

Drug	2007	2008	2009	2010	2011
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Drug	2007	2008	2009	2010	2011
ethinylestradiol/ levonorgestrel	304,890	1,078,000	1,090,000	1,102,000	432,070

Data on prescriptions on brand-level of oral contraceptives for the period 2004-2007 are given in a publication by the Foundation for Pharmaceutical Statistics (SKF) [11]. See figure 1.

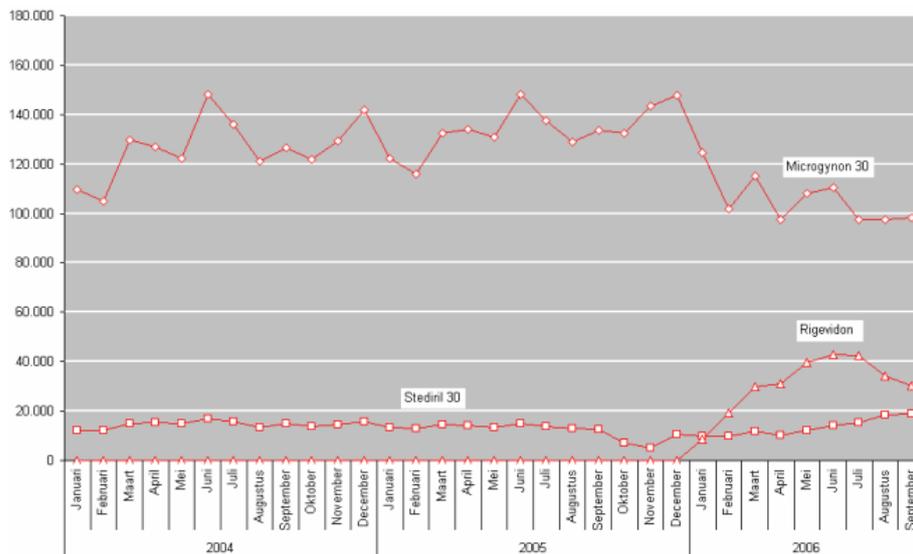


Figure 1: The number of prescriptions of Microgynon 30, Rigevidon and Stedini 30 per month.

Mechanism

Drug-substitution mostly entails substitution of branded medicines by cheaper generic medicines. The way the Medicines Evaluation Board (MEB) approves generics is based on assessment of the quality of the medicine and bioequivalence testing according to strict European guidelines [12,13]. Possibly, small variances in bioequivalence could play a role in the occurrence of the reported adverse drug reactions for some patients.

Discussion and conclusion

With this quarterly report Lareb wishes to give information about the adverse drug reactions that were reported in association with substitution between “one-phase” oral contraceptive pills containing ethinylestradiol/levonorgestrel.

Lareb received 149 reports of adverse drug reactions related to substitution of one oral contraceptive pill by another oral contraceptive pill with the ATC code G03AA07. The number of reports per drug on the level of the HPK-code was the highest for Rigevidon® (87 reports) and ethinylestradiol/levonorgestrel 0,03/0,15 Apothecon® (40 reports), which are the same product with a different name.

Of the 149 received reports, 55 included the MedDRA® Lower Level Term (LLT) break-through bleeding as an adverse drug reaction. The majority of reports about break-through bleeding that Lareb received occurred after switch Microgynon 30® to Rigevidon® (29 reports) and ethinylestradiol/levonorgestrel 0,03/0,15 Apothecon® (12 reports).

There were 172 other reported adverse drug reactions besides break-through bleeding, with gastro-intestinal complaints and headache being the most reported reactions.

An overview about the Rigevidon® reports, including reports of break-through bleeding, was sent to the MEB in 2006 [1].

The Reporting Odds Ratio for “Therapeutic response unexpected with drug substitution” is disproportional for the “one phase” oral contraceptives containing ethinylestradiol/levonorgestrel, meaning that reactions after drug-substitution are more often reported for this group than for other drugs. For this overview on reactions after drug substitution it could be possible that changes in reimbursement status or media attention have an effect on the rate of adverse drug reaction reporting, leading to a so called ‘Notoriety-bias’ [14].

Lareb will stay vigilant of any new reports of adverse reaction in association with substitution between these oral contraceptives.

- Overview of reports after drug substitution between “one-phase” oral contraceptives containing ethinylestradiol/levonorgestrel
- Majority of the reports in this overview are about the product of one Marketing Authorization Holder

References

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This signal has been raised on November 2012. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).